P-21: Biophysics

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Introduction

The Biophysics Group (P-21) was founded in 1988 with the goal of applying the scientific and technical resources of Physics Division to the biosciences. The mission of P-21 is to apply physics knowledge and techniques to increase our understanding of important biological phenomena and to use biological systems to elucidate physical principles of complex phenomena. The group has strengthened existing biological projects within the Division and has initiated new bioscience efforts in a number of directions. Group members are engaged in biophysical research over a wide range of physical scales, including characterization of the structure and dynamics of protein molecules and the implications of those qualities for protein function; ultrasensitive detection and characterization of individual molecules using laser fluorescence; design and implementation of biologically inspired robots and adaptive digital hardware; development, validation, and application of noninvasive techniques for the measurement of human brain function; development of nonbiological applications of low-field magnetic sensors; and development of three-dimensional computational models of the human brain.

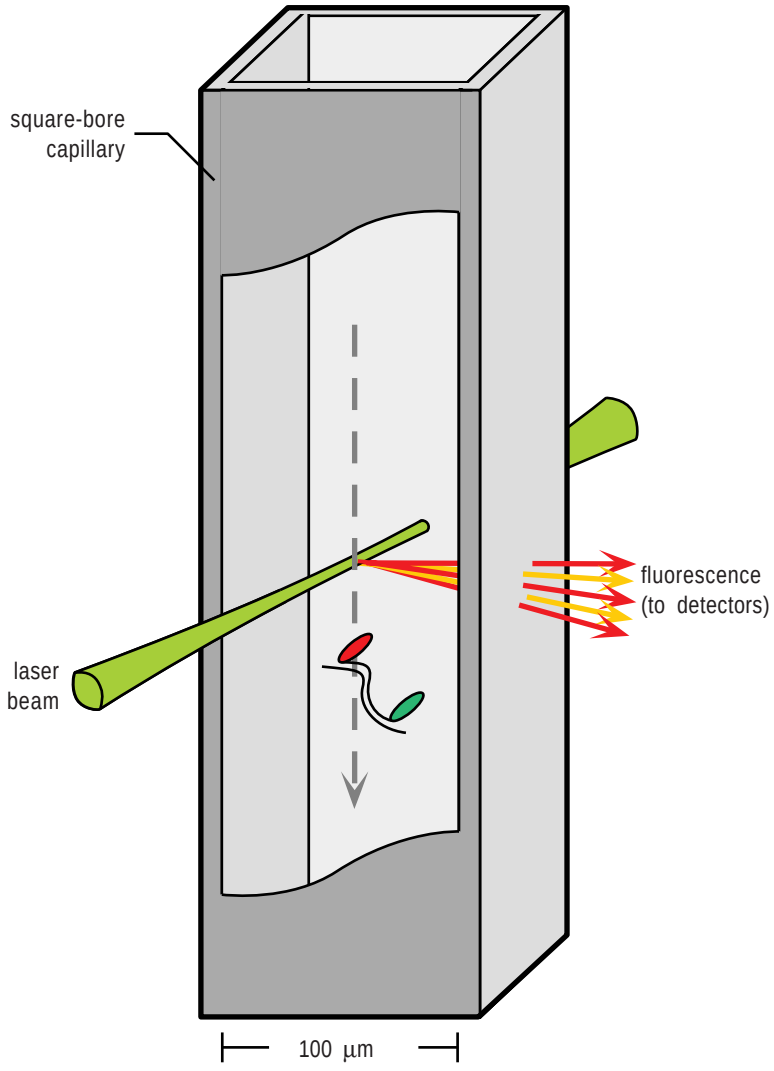

Fig. I-1. Two nucleic-acid probes that complement a targeted sequence are labeled with different fluorescent markers. If the target molecule is present, both probes will bind to the target and reveal it by responding simultaneously when illuminated by the laser-based, ultrasensitive fluorescence system.

Single-Molecule Detection

P-21 and its collaborators have extended their work on the detection and characterization of single molecules in a liquid. The goal of this research is to measure and characterize the spectroscopic properties of individual molecules. Such spectroscopic measurements can be used to identify the presence of a particular molecular species in an extremely dilute solution, or they can be used to probe the local environment that surrounds an individual molecule. The former capability promises a new level of speed and sensitivity for medical diagnostics, whereas the latter capability makes it possible to study properties of biological systems that cannot be measured when a lack of sensitivity confines measurements to the determination of the average properties of a large ensemble of microenvironments. Thus far, the spectroscopic properties measured at the single-molecule level include emission spectra, fluorescence lifetime, and total emission intensity. Recently the single-molecule spectroscopic approach has been extended to include single-molecule electrophoresis and approaches to ultrasensitive detection of viral and bacterial pathogens in soil and water samples. We are exploring additional applications for basic research and for medical diagnostics (Fig. I-1).

Protein Dynamics Studies

The goals of P-21 studies of protein dynamics are to describe protein motion in atomic detail and to understand the consequences of dynamics for protein function. Our approach is to bring crystals of the CO-complex of the protein myoglobin down to liquid-helium temperatures, photolyze the CO with a flash of light, and observe the subsequent rebinding reaction with x-ray crystallography. We have constructed and tested a low-temperature Laue camera, determined the freezing conditions for the CO crystal that maintain the high degree of order required for Laue diffraction, and analyzed diffraction patterns obtained at 5 K. The results of this approach have accomplished the long-sought goal of characterizing the changes in the three-dimensional structure of a protein as it binds to a ligand (I. Schlichting, J. Berendzen, G. N. Phillips, and R. M. Sweet, "Crystal Structure of Photolyzed Carbonmonoxy-myoglobin," *Nature* **371**, 808 [1994]).

Cryo-Crystallography

Cryo-crystallography is being extended to studies of electron transfer in the photosynthetic reaction center and to the understanding of proteins important for bioremediation of trichloroethylene (TCE) and other soil and groundwater pollutants. P-21 is part of a multidisciplinary Los Alamos effort that seeks to enable bioremediation of TCE by genetically engineered microorganisms. The first step in this effort is obtaining a thorough understanding of the enzymatic mechanisms by which TCE can be degraded. We would like, in effect, to watch proteins at work chewing up TCE. In a collaboration with scientists at U.S. universities and at the Max Planck Institute in Germany, members

of P-21 have begun to unravel the mystery surrounding the mechanism of one class of enzymes that might be engineered to degrade TCE, the cytochrome P-450s. P-450s bind molecular oxygen, split the dioxygen bond, and insert one oxygen atom into organic substrates. This can be the first step in the biodegradation of TCE. The reaction is also a crucial step in steroid hormone synthesis, and P-450s are important targets for drugs to treat breast cancer and other malignancies.

Noninvasive Imaging Techniques

The P-21 neuroscience effort focuses on the use of magneto-encephalography (MEG) and magnetic resonance imaging (MRI) to develop improved techniques for noninvasive imaging of the human brain. MEG involves the use of superconducting quantum interference devices (SQUIDs) to measure magnetic fields associated with human-brain activity. Measurement of the magnetic fields of the brain (which are approximately a billion times smaller than that of Earth) requires sensitive magnetic sensors, magnetic shielding from the environment (currently implemented through a shielded room), and advanced signal-enhancement and modeling techniques. Because magnetic fields readily penetrate the skull, MEG offers the potential for non-invasive measurement of brain function in much the same way that computed tomography and MRI allow the noninvasive detection of brain structure. MEG has therefore generated considerable interest in its possible use as a tool in basic neuroscience for functional mapping of the human brain (Fig. I-2), as a clinical tool for the assessment of neurological and psychiatric disorders, as a possible source of signals for use in the development of neural prosthetics and human-machine interfaces, and in other applied contexts. Group members are engaged in projects to design improved multichannel magnetic sensors, to develop more accurate mathematical models for localizing the electrical and magnetic signals from the brain, to validate MEG using known current sources in computational and physical models of the brain, and to

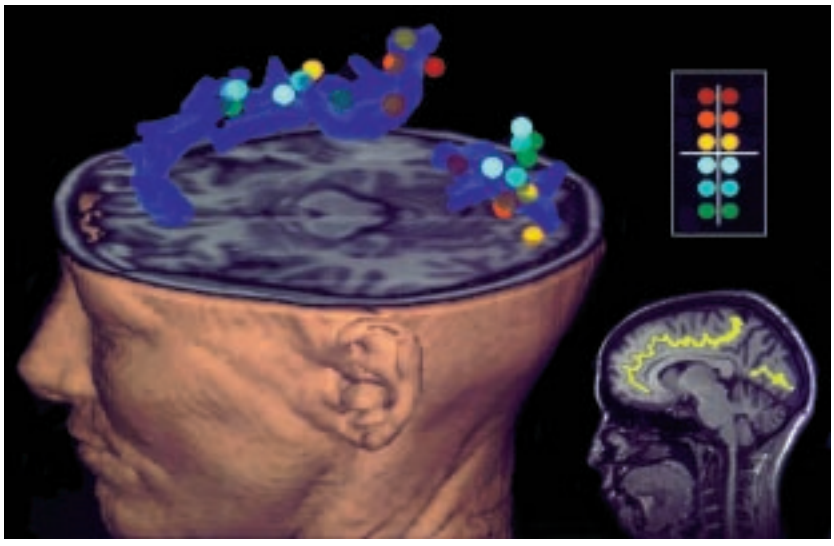

Fig. I-2. The small, colored spheres represent active regions of the cortex along the cingulate sulcus and the calcarine fissure (upper and lower blue structures, respectively) that are responding to small patterns of light from various positions in the visual field (see corresponding spheres in the inset). Systematic mapping is evident: stimuli placed in the upper visual field activated posterior regions of the cingulate sulcus and lower regions of the calcarine fissure; lower-field stimuli activated anterior regions of the cingulate and upper regions of the calcarine.

use MEG to address important questions in basic neuroscience and in research on neurological and psychiatric disorders. Many of P-21's neuroscience projects are conducted in collaboration with the New Mexico Institute of Neuroimaging, a consortium that includes Los Alamos, the University of New Mexico, and the New Mexico Regional Federal Medical Center and is sponsored by the U.S. Department of Veterans Affairs.

Combining MEG and anatomical MRI with other functional imaging techniques such as functional MRI (fMRI) and positron emission tomography (PET) offers the opportunity of increasing the combined spatial and temporal resolution of functional imaging techniques well beyond that of any single method. P-21 is engaged in developing mathematical models for combining these alternative forms of brain imaging. This work is part of a nationwide effort to develop three-dimensional computational models of the brain in which a variety of structural and functional information can be represented for storage, retrieval, and analysis.

Low-Field Magnetic Sensors

The P-21 low-field magnetic sensor effort has recently been extended to apply low-field sensors to nondestructive evaluation (NDE) of materials, detection of underground objects, and a number of applications in nonproliferation. These applications take advantage of a number of recent Los Alamos developments, including new concepts in superconducting weak-field sensor arrays, the introduction of digital signal processors (DSPs) into the SQUID circuit, and improved high-temperature superconducting (HTS) Josephson junctions for HTS SQUIDs. The resulting sensors will be designed to operate in relatively hostile electromagnetic environments.

Adaptive Control Systems

P-21 has begun investigations into the design, implementation, and application of a variety of adaptive control systems. These include development of biologically inspired, legged robotics with simple, highly robust control circuits (Fig. I-3); applications of wavelets for feature recognition and data compression; and support for advanced multichannel data-acquisition systems. This work promises to contribute both to an improved understanding of robotic control and to a variety of applications in which robust, inexpensive adaptive capabilities are required.

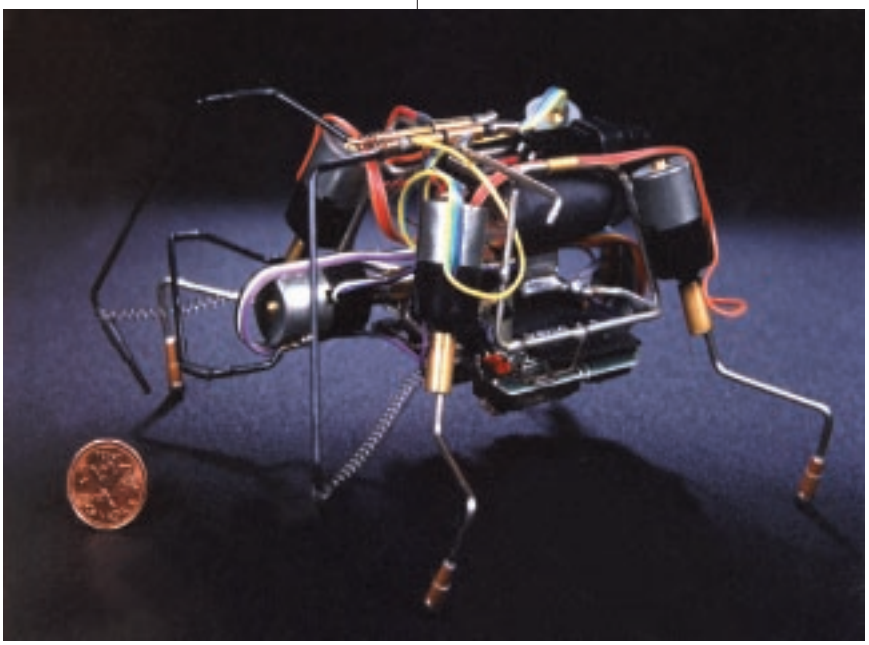

Fig. I-3. Turtle 1.5, a first-generation "biomech" walker, self-optimizes its gait over various terrains, even after considerable damage. Its analog control system adapts to such situations without the need of any programming.